Rejections Under 35 U.S.C. § 101

The Examiner has maintained his rejection of claims 27 - 46 under 35 U.S.C. § 101. According to the Examiner, based on the reasons set forth in Paper No. 5, the claimed invention is supported by neither a credible, substantial and specific asserted utility, nor a well-established utility. Applicants respectfully traverse the rejection.

At the outset, Applicants respectfully submit that the PTO cannot properly make and sustain this type of rejection unless it has reason to doubt the objective truth of the statements contained in the written description. *See, In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) ("[T]he PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.") (citations omitted); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) ("[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."). The PTO may establish a reason to doubt an invention's asserted utility when the written description "suggest[s] an inherently unbelievable undertaking or involve[s] implausible scientific principles." *Brana*, 34 USPQ2d at 1441; see also *In re Eltgroth*, 419 F.2d 918, 164 USPQ 221 (CCPA 1970).

At page 2, item 5, of Paper No. 16, the Examiner contends that: "there is no evidence of record that a receptor protein of the claimed invention is associated in any way with a specific disease or disorder. Apoptosis is not a disease or disorder. It is a fundamental process known to occur in multicellular organisms. However, there is no reference of record which describes the employment of a death domain-containing receptor to effect apoptosis for clinical effect."

Applicants submit that the Examiner has not provided references or provided sound scientific reasoning or evidence to substantiate his belief that those skilled in the art would "reasonably doubt" Applicants' asserted utility concerning apoptosis. Further, the Examiner has not established that Applicants' asserted utility is inherently unbelievable or involves implausible scientific principles.

Applicants have provided evidence that the claimed proteins are integrally involved in the process of apoptosis (programmed cell death). As indicated in the present application and well-recognized by those skilled in the art at the time the present application was filed, disruption or inappropriate regulation of apoptosis has profound pathological consequences. *See*, specification at page 3, lines 14-16 ("Derangements of apoptosis contribute to the pathogenesis of several human diseases including cancer, neurodegenerative disorders, and acquired immunodeficiency syndrome."); *See also* specification at page 38, line 18, to page 39, line 2 (describing various diseases associated with increased or decreased apoptosis). Therefore, although apoptosis is "not a disease or disorder," *per se*, it is a physiological and biological mechanism whose dysregulation can lead to a number of pathogenic processes.

In this regard, Applicants' disclosure indicates that the present invention is useful for the treatment of diseases associated with de-regulated or abnormal apoptosis. *See*,

specification at page 39, lines 3-19. Among such diseases specifically mentioned are cancers such as follicular lymphomas. *See*, specification at page 38, lines 18-19. Importantly, recent results confirm a link between DR3 and follicular lymphoma. *See* Warzocha *et al.*, BIOCHEM. BIOPHYS. RES. COMMUN. 242:376-379 (1998) (copy provided along with the Reply to Final Office Action filed on February 20, 2001). Warzocha describes the isolation of an isoform of DR3 from mRNAs of a panel of human cell lines and tumor tissues obtained from patients with follicular non-Hodgkin's lymphoma. These results strongly suggest that DR3 functions to participate in lymphoid cell homeostasis. *See id.* at page 379 ("the 'programmed' change in DR3 alternative splicing may have functional effects not only in lymphocyte activation but also in lymphocyte differentiation and malignant transformation."). Applicants have disclosed diseases and conditions associated with the claimed receptors and thus have defined a "real world context of use."

In Paper No. 16, the paragraph bridging pages 3 and 4, however, the Examiner contends, essentially, that the Warzocha paper cannot be used to support utility as it was published after the filing date of the present application. Specifically, the Examiner states, "... an invention must be patentable at the time that an application is filed ('in currently available form'). Applicants can not rely upon subsequent discoveries by themselves or others to perfect the claimed invention." Applicants respectfully, but emphatically, disagree with this position because a post-filing date publication certainly may be used to support an originally asserted utility.

Applicants direct the Examiner's attention again to the *Brana* decision. In *Brana*, 34 USPQ2d 1436, 1441, the Federal Circuit noted that the Applicants had provided post-filing date test results in the form of a declaration by Dr. Michael Kluge showing that several

compounds within the scope of the claims exhibited significant anti-tumor activity. The Federal Circuit went on to clarify that although the declaration was dated *after* the Applicant's filing date, it can still be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. Specifically, the *Brana* court stated, "[i]t does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id.* at footnote 19.

Similarly, in the present case, the Warzocha post-filing date publication can be properly used to support and prove that the originally asserted utility present in the specification at the filing date, was in fact accurate when filed.

The Examiner goes on to state that: "The fact that Applicant included lymphomas in a long list of causally unrelated diseases does not constitute either a specific or credible assertion on a utility for the claimed protein." Paper No. 16, page 4, lines 3-5. Applicants respectfully disagree with this characterization.

On page 38, lines 18-25, of the present specification, Applicants state that diseases associated with increased cell survival, or the inhibition of apoptosis, include four main groups of disorders: (1) cancers; (2) autoimmune disorders; (3) viral infections; and (4) graft rejection. Applicants provided several examples within these four classes. Follicular lymphoma was listed as an exemplary cancer. Hardly, this is a "long list of causally unrelated diseases." Rather, these four diseases share a common, inherent characteristic of inhibited apoptosis, or, in other words, excessive cell proliferation or survival, along with impaired regulation of the immune system. *See*, present specification, page 5, 20-26, and

page 43, lines 23-25. Applicants also teach how the claimed proteins can be administered in order to enhance apoptosis. *See*, present specification, page 39, lines 3-11. Moreover, an assertion of multiple utilities, even if the Examiner does not accept one, does not prejudice an accurately asserted utility. *See, Krantz v. Olin*, 356 F2d 1016, 1019, 148 USPQ 659, 662 (CCPA 1966).

Disclosure by Applicants regarding diseases associated with the *inhibition* of apoptosis, and in particular, the express recitation of follicular lymphomas as an example, was also present in the earliest priority application, Application No. 60/013,285, filed March 12, 1996. *See*, page 34, lines 15-23 of the '285 application.

Further, in order to treat diseases and disorders associated with decreased apoptosis (caused, *e.g.*, by insufficient levels of DR3), agonists of DR3 may be used. Antibodies directed against the DR3 polypeptide are an example of such agonists. *See*, present specification, page 39, lines 3-11, as well as priority provisional application app. no. 60/013,285, page 34, line 32 to page 35, line 3.

The use of the DR3 protein, independent of an identified ligand, is further demonstrated in Example 6 of the specification where high levels of DR3 in a cell -- simulating DR3 activation -- was shown to cause apoptosis (these results are discussed in more detail below). Thus, the claimed proteins possess sufficient utility under 35 U.S.C. § 101 regardless of whether the identity of the corresponding ligand is known or unknown.

Applicants respectfully submit that the Examiner is applying an inappropriately high burden to satisfy the requirement for utility, which is contradictory to established law. While Applicants have done more, as detailed above, even the mere identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and,

therefore, satisfies the utility requirement. The CCPA (the predecessor of the Federal Circuit) has stated:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility.

Nelson v. Bowler, 206 U.S.P.Q. 881, 883 (CCPA 1980). *See*, also, *In re Krimmel*, 130 U.S.P.Q. 215, 219 (CCPA 1961)("[O]ne who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.")

The Federal Circuit has also addressed the issue of pharmacological utility. In so doing the Federal Circuit has recognized that:

> FDA approval . . . is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

In re Brana, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Demonstration of a pharmacological effect is sufficient to satisfy the requirement for utility. Apoptosis is such a pharmacological effect. Utility does not require clinical efficacy in humans. The Examiner is treating the present claims as if they were a method for curing

or treating lymphoma. In any event, Applicants have gone as far as linking the present invention to follicular lymphoma.

The Examiner asserts that "the art has yet to describe the successful employment of [the] TNF receptor as the target of a clinically useful ligand." While this assertion is not relevant (see analysis above), Applicants respectfully note that the assertion is also not accurate. Specifically, there are drugs currently on the market, that are derived from tumor necrosis factor (TNF) receptors. For example, Enbrel™ is a pharmaceutical manufactured by Immunex Corporation and Wyeth-Ayerst Pharmaceuticals that is sold for the treatment of rheumatoid arthritis ("RA").

Although TNF is involved in normal and inflammatory responses, elevated levels of TNF have been found in the synovia fluid and joints of RA patients. Enbrel™ is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG1. Enbrel™ works by binding specifically to TNF and blocking its interaction with cell surface TNF receptors, rendering the TNF biologically inactive. *See*, Exhibit A, attached herewith.

In the present application, as well as the prior applications, Applicants also taught that soluble forms of DR3 fragments that include the ligand binding domain from the extracellular domain of the DR3 receptor could be used as an antagonist to limit or inhibit apoptosis in an analogous manner. *See*, present specification, page 43, lines9-11 as well as priority provisional application app. no. 60/013,285, page 39, lines 13-16.

Finally, Applicants have shown that DR3-induced apoptosis was blocked when reagents were included that had been previously shown to inhibit apoptosis induced by the TNF receptor family members TNFR-1 and Fas/APO-1. *See*, specification at page 72, lines

3-7 ("DR3-induced apoptosis was blocked by the inhibitors of ICE-like proteases, CrmA and z-VAD-fmk [and by] dominant negative versions of FADD ... or FLICE"). The results described in the specification demonstrate that DR3-induced cell death is not caused by a non-specific effect, but rather, is the result of the highly coordinated biological process of apoptosis. Since apoptosis is a specific biological consequence directly associated with DR3, the claimed proteins of the instant application possess specific, substantial and credible utility.

In summary, Applicants reiterate that the proteins of the present invention possess specific, substantial, and credible utilities. The claimed DR3 polypeptides have been shown to induce apoptosis. Consistent with these results, the claimed polypeptides are useful for, among other things, the treatment of diseases associated with "derangements of apoptosis," including, for example, follicular lymphoma. The asserted utilities are *specific* because the induction of apoptosis is specific to the claimed invention and is not applicable to the broad class of the invention (*i.e.*, not all receptors are involved with the process of apoptosis, or follicular lymphoma, for example). In addition, the asserted utility is *substantial* because abnormal apoptosis is associated with diseases and conditions, such as, *e.g.*, follicular lymphoma, and the claimed proteins (as well as agonist or antagonist compounds), can be used to treat such diseases. Finally, the asserted utility is *credible* because use of the claimed proteins to treat diseases associated with abnormal apoptotic properties would be believable to one skilled in the art. The results of Warzocha *et al.*, *supra*, implicating DR3 in follicular non-Hodgkin's lymphoma, *confirm* the credibility of Applicants' asserted utilities in this context. The usage of an FDA approved drug, Enbrel™, for treatment of RA,

that is derived from the extracellular ligand-binding portion of the TNF receptor, further supports the credibility of Applicants' asserted utilities.

In view of the arguments set out above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-46 under 35 U.S.C. § 101.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained his rejection of claims 27 - 46 under 35 U.S.C. § 112, first paragraph. The Examiner contends that since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well-established utility, for the reasons above with regards to the rejection under 35 U.S.C. § 101, one skilled in the art would not know how to use the claimed invention. *See* Paper No. 16, page 4.

Applicants respectfully disagree with this ground of rejection and note that this rejection has been sufficiently addressed above with regard to the rejection of these claims under 35 U.S.C. § 101.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-46 under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 102(b)

The Examiner rejects claims 27-46 under 35 U.S.C. § 102 (b) as being anticipated by each of the Chinnaiyan *et al.* and Kitson *et al.* November 1996 publications. Paper No. 16, page 5. In short, the Examiner contends that these publications are prior art because the

priority applications of the present case are unavailable under 35 U.S.C. § 120. The Examiner's rationale is that because the present case doesn't meet the requirements of 35 U.S.C. § 112, first paragraph, then the prior application also does not meet those requirements. Applicants respectfully traverse this rejection.

As discussed above, Applicants believe that the requirements of 35 U.S.C. § 112, first paragraph, have been satisfied for both the present application and its earlier parental applications. Accordingly, Applicants submit that the Chinnaiyan *et al.* and Kitson *et al.* publications are not available as prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution and allowance of this application, the Examiner is invited to telephone the undersigned at the number provided. If the Examiner does not believe that the case is in condition for allowance, Applicants respectfully request a personal interview with the Examiner.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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